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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/751,826	CASTERMAN ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-36,51-59 and 64-69* is/are pending in the application.

4a) Of the above claim(s) *23,24,28-30,34,36,55-59 and 64-69* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-22, 25-27, 31-33, 35, 51-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/23/07 has been entered.

Applicant's amendment and response filed 4/23/07 is acknowledged and has been entered.

2. Applicant is reminded of Applicant's election of Group I (claims 18-36 and 51-59), and species of fragment of an immunoglobulin which is the variable region of a heavy chain, said variable region devoid of normal light chain interaction sites, and Applicant's election with traverse of the species of "labeled with a detectable label" that is "a radioactive label" in Applicant's response filed 1/23/06.

Claims 18-21, 25-27, 31-33, 35 and 51-54 read upon the elected species.

Applicant is reminded that upon consideration of the prior art, the search had been extended to include the species recited in instant claim 22, *i.e.,* "immunoglobulin or a fragment thereof according to claim 19, which has a constant region which is devoid of a CH1 domain."

3. Applicant is reminded that since Applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for the prosecution on the merits. Accordingly, claims 64-69 are withdrawn from consideration as being directed to non-elected inventions. See 37 CFR 1.142(b) and MPEP 821.03.

Newly submitted claims 64-69 are directed to inventions that are independent or distinct from the invention originally claimed for the following reasons:

Group XIII. Claims 64 and 65 are drawn to a method for synthesizing an immunoglobulin or fragment thereof, classified in Class 435, subclass 69.7,

Group XIV. Claims 66, 67 and 68 are drawn to a nucleic acid molecule encoding an immunoglobulin or fragment thereof classified in Class 536, subclass 23.53, a vector comprising said nucleic acid classified in Class 435, subclass 320.1, and a host cell transfected with said vector classified in Class 252.3, respectively,

Claim 69 is drawn to a method of treating and/or preventing disease in a patient classified in Class 424, subclass 141.1, and links non-elected Groups VIII and IX.

Inventions XIII and I are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make another and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case the product as claimed can be made either as a conjugate by chemical conjugation or as a fusion protein by expression in a host cell.

Inventions I and XIV are directed to related inventions. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, *i.e.,* are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design in that the immunoglobulins of Group I are comprised of amino acid residues whereas the nucleic acid molecule and vector thereof are comprised of nucleotide bases. The host cell of Invention XIV is comprised of proteins, nucleic acid molecules, lipids and subcellular structures and organelles. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

Accordingly, claims 23, 24, 28-30, 34, 36 and 55-59 (non-elected species of Group I) remain withdrawn and newly added claims 64-69 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Claims 18-22, 25-27, 31-33, 35 and 51-54 are currently being examined.

4. Applicant is reminded that Applicant is required to amend the specification to list the appropriate SEQ ID NOS for sequences disclosed in the specification (for example, on page 16 at line 16 for $CTCGAGT_{12}$). See 37 C.F.R. 1.821(d)

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 18-22, 25-27, 31-33, 35 and 51-53 are rejected under 35 U.S.C. 102(b) as being anticipated by Ungar-Waron *et al* (Isr. J. Vet. Med. 1987, Vol. 43(3), pages 198-203, IDS reference) as evidenced by Hamers-Casterman *et al* (Nature 3 June 1993, Vol. 363, pages 446-448, IDS reference), Roux *et al* (PNAS USA 1998, Vol. 95, pages 11804-11809, IDS reference), WO 94/25591 (Applicant's IDS reference in the Form-1449 filed 7/24/06), van der Linden *et al* (Biochimica et Biophysica Acta 1999, 1431: 37-46, of record), and EP 0739981 A1 (of record).

Ungar-Waron *et al* teach a 40 Kd IgG from Camelid serum and composition thereof. Ungar-Waron *et al* teach that when camel serum was precipitated using ammonium sulfate, separated by DEAE-Sephacel, subjected to ultrafiltration, and analyzed by IEP and by SDS-PAGE two bands of 155 Kd and 100 Kd were visualized under non-reducing conditions, the 100Kd band dissociating into the 40 Kd band under reducing conditions upon SDS-PAGE analysis (especially Results and Discussion sections).

Evidentiary reference Hamers-Casterman *et al* teach VHH (V for variable region of heavy chain) from *Camelid* (infected with trypanosomes) serum that bind a large number of antigens present in a ^{35}S methionine-labeled trypanosome lysate, said VHH consisting of heavy-chain VHH dimers devoid of light chains and lacking the CH1 domain that binds to the light chain. Hamers-Casterman *et al* teach that the two 100 Kd immunoglobulin fractions yield only heavy chains of 46 Kd and 43 Kd upon reduction (see entire article, and especially second paragraph of article).

Evidentiary reference Roux *et al* teach that in *Camelids*, two of their three IgG subclasses contain no light chains and the unassociated VH domains interact with antigen as monomers (especially page 11804, column 2, paragraph before Materials and Methods section).

Evidentiary reference WO 94/25591 teaches the presence of considerable amounts of IgG like material of 100 Kd in the serum of the camel and that these molecules are composed of heavy chain dimers and are devoid of light chains. WO 94/25591 further teaches that these molecules bear an extensive antigen binding repertoire, and that camel heavy chain IgGs lack the CH1 domain, which in one IgG class might be structurally replaced by an extended hinge. WO 94/25591 teaches that heavy chain IgGs are a feature of all *Camelids*. WO 94/25591 teaches that by a combination of affinity chromatography on Protein A and Protein G, three quantitatively important fractions corresponding to subclasses of IgG can be isolated from the serum of camels, two of which contain molecules of about 100 Kd, which upon reduction yield only heavy chains of 46 Kd (IgG2 fraction binding only to Protein A) and 43 Kd (IgG3 fraction binding to Protein A and Protein G), and both classes lack the light chain completely (see entire reference, especially page 1 at lines 18-32, page 2 at lines 1-4).
WO 94/25591 teaches that this 100 Kd IgG like material is the same as taught by Ungar-Waron et al (the art reference cited in this rejection, see page 1 at lines 18-19 and page 4 at lines 31-32).

Although the art reference Ungar-Waron *et al* does not teach that the 40 Kd IgG band from *Camelid* serum contains VHH lacking CH1 and devoid of light chains or binds antigens such as those recited in instant claim 53:

- evidentiary reference Hamers-Casterman *et al* teach the approximately 40 Kd size of the VHH lacking CH1 and devoid of light chains in *Camelid* serum upon reduction of the 100 Kd IgG that bind antigens in a lysate containing proteins, carbohydrates and nucleic acids from an infectious agent and that some *Camelids* have high anti-trypanosome titers,
- Roux *et al* teach that in *Camelids*, two of their three IgG subclasses contain no light chains and the unassociated VH domains interact with antigen as monomers, and
- WO 94/25591 teaches that the 100 Kd fraction of the art reference Ungar-Waron *et al* contains *Camelid* IgG heavy chains that lack light chains, lack the CH1 domain, and that these heavy chains bind antigens.

Therefore the claimed antibody appears to be the same as the antibody of the prior art absent a showing of differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show a distinction between the antibody of the instant invention and that of the prior art. See *In re* Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Evidentiary reference van der Linden *et al* teach that that the IgG *Camelid* heavy chain antibody is devoid of the immunoglobulin light chain. van der Linden *et al* further teach that the variable fragments of heavy chain antibodies (VHH) do not have the hydrophobic interface which is important in the formation of a functional "classical" antibody molecule, composed of heavy and light chains (page 38 at the first full paragraph at column 1). van der Linden *et al* teach that unique features of VHH include the absence of both immunoglobulin light chains and the CH1 constant domain, and that camelid VHH have been shown to retain immunoglobulin functions such as specific antigen binding (paragraph spanning pages 43-44).

With regard to the recitation of "said variable region being devoid of normal light chain interaction sites" in instant claims 18, 19, 51 and 52, although the art reference Ungar-Waron *et al* does not teach that the *Camelid* IgG comprises a variable region devoid of normal light chain interaction sites, the evidentiary reference van der Linden *et al* teach that the *Camelid* variable fragments of the heavy chain antibodies do not have the hydrophobic interface which is important in the formation of a functional classical antibody molecule that is composed of heavy and light chains. Therefore the claimed antibody appears to be the same as the antibody of the prior art absent a showing of differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show a distinction between the antibody of the instant invention and that of the prior art. See *In re* Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Evidentiary reference EP 0739981 A1 teaches that the superior solubility of Camelid VH domain along with its small size and amino acid sequence of the framework region that is very homologous to that of human, ensure a minimum of immunogenicity when administered to humans (especially page 11 at lines 14-23), *i.e.,* that it is "suitable for use in *in vivo* diagnosis" recited in instant claim 32.

However, claims 31 and 32 are also included in this rejection because the intended uses of the immunoglobulin "suitable for use in *in vitro* diagnosis" or "suitable for use in *in vivo* diagnosis", respectively, do not carry patentable weight per se.

Claims 51 and 52 are included in this rejection because the art reference teaches partially purified and substantially purified fractions containing of IgG from *Camelid* sera, *i.e.,* a "composition comprising an Immunoglobulin or fragment thereof..."
Claims 33 and 35 are included in this rejection because the art reference teaches the antibody labeled with a protein stain, *i.e.,* a detectable label that is a chemical label.

Claims 25-27 are included in this rejection because the recitation of a method wherein the claimed product is made carries no patentable weight in these product claims.

The instant claims that recite "fragment thereof" are included in this rejection because the 40 Kd band taught by the art reference is a fragment of a divalent immunoglobulin that binds antigen as evidenced by WO 94/25591.

Applicant has not addressed this rejection.

7. Claims 18-22, 25-27, 31-33, 35 and 51-53 are rejected under 35 U.S.C. 102(b) as being anticipated by Grover *et al* (Ind. J. Biochem. Biophys. 1983, 20(4): 238-240, IDS reference filed 7/24/06, of record) as evidenced by WO 94/25591 (IDS reference filed 7/24/06), Satija *et al* (Inf. Immun. 1979, 24(2: 567-570, of record), van der Linden *et al* (Biochimica et Biophysica Acta 1999, 1431: 37-46, of record), and EP 0739981 A1 (of record).

Grover *et al* teach camel IgG2 isotype polyclonal antibodies, including in reduced form. Grover *et al* teach that polyacrylamide gel electrophoresis of ammonium sulfate precipitated camel serum immunoglobulins was done as described by Satija *et al* in Inf. Immun. 1979, 24(2): 567-570, (especially pages 238-239 of Grover *et al*).

Evidentiary reference WO 94/25591 teaches the presence of considerable amounts of IgG like material of 100 Kd in the serum of the camel and that these molecules are composed of heavy chain dimers and are devoid of light chains. WO 94/25591 further teaches that these molecules bear an extensive antigen binding repertoire, and that camel heavy chain IgGs lack the CH1, which in one IgG class might be structurally replaced by an extended hinge. WO 94/25591 teaches that heavy chain IgGs are a

feature of all *Camelids*. WO 94/25591 teaches that by a combination of affinity chromatography on Protein A and Protein G, three quantitatively important fractions corresponding to subclasses of IgG can be isolated from the serum of camels, two of which contain molecules of about 100 Kd, which upon reduction yield only heavy chains of 46 Kd (IgG2 fraction binding only to Protein A) and 43 Kd (IgG3 fraction binding to Protein A and Protein G), and both classes lack the light chain completely (see entire reference, especially page 1 at lines 18-32, page 2 at lines 1-4).

Evidentiary reference Satija *et al* teach that polyacrylamide electrophoresis involved staining the gel with a solution of amido black in HAc (*i.e.,* labeled with a detectable label that is a chemical marker as recited in instant claims 33 and 35, respectively, materials and methods section).

Although the art reference Grover *et al* does not teach that the IgG2 istoype antibody from *Camelid* serum contains VHH lacking CH1 and devoid of light chains, or binds antigens such as those recited in instant claim 53, evidentiary reference WO 94/25591 teaches that the *Camelid* IgG2 heavy chains lack light chains and that these heavy chains bind antigens. Therefore the claimed antibody appears to be the same as the antibody of the prior art absent a showing of differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show a distinction between the antibody of the instant invention and that of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Evidentiary reference van der Linden *et al* teach that that the IgG *Camelid* heavy chain antibody is devoid of the immunoglobulin light chain. van der Linden *et al* further teach that the variable fragments of heavy chain antibodies (VHH) do not have the hydrophobic interface which is important in the formation of a functional "classical" antibody molecule, composed of heavy and light chains (page 38 at the first full paragraph at column 1). van der Linden *et al* teach that unique features of VHH include the absence of both immunoglobulin light chains and the CH1 constant domain, and that camelid VHH have been shown to retain immunoglobulin functions such as specific antigen binding (paragraph spanning pages 43-44).

With regard to the recitation of "said variable region being devoid of normal light chain interaction sites" in instant claims 18, 19, 51 and 52, although the art reference Grover *et al* does not teach that the IgG2 istoype antibody from *Camelid* serum comprises a variable region that is devoid of normal light chain interaction sites, the evidentiary reference van der Linden *et al* teach that that the IgG *Camelid* heavy chain antibody is devoid of the immunoglobulin light chain and that the variable fragments of these heavy chain antibodies (VHH) do not have the hydrophobic interface which is important in the formation of a functional "classical" antibody molecule, composed of heavy and light chains. Therefore the claimed antibody appears to be the same as the antibody of the prior art absent a showing of differences. Since the Patent Office does not have the

facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show a distinction between the antibody of the instant invention and that of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Evidentiary reference EP 0739981 A1 teaches that the superior solubility of Camelid VH domain along with its small size and amino acid sequence of the framework region that is very homologous to that of human, ensure a minimum of immunogenicity when administered to humans (especially page 11 at lines 14-23), *i.e.,* that it is "suitable for use in *in vivo* diagnosis."

However, claims 31 and 32 are also included in this rejection because the intended uses of the immunoglobulin "suitable for use in *in vitro* diagnosis" or "suitable for use in *in vivo* diagnosis", respectively, do not carry patentable weight per se.

Claims 51 and 52 are included in this rejection because the art reference teaches a partially purified fraction containing of IgG from *Camelid* sera, *i.e.,* a "composition comprising an Immunoglobulin or fragment thereof..."

Claims 25-27 are included in this rejection because the recitation of a method wherein the claimed product is made carries no patentable weight in these product claims.

Applicant has not addressed this rejection.

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 18-22, 25-27, 31, 32 and 51-54 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 18-27 of copending Application No. 11/350,900. Although the conflicting claims are not identical, they are not patentably distinct from each other because the VHH IgG2 istoype recited in the claims of copending '900 are encompassed by the VHH of the instant claims (which encompass IgGg2 and IgGg3 isotypes) as evidenced by van der Linden *et al* (Biochimica et Biophysica Acta 1999, 1431: 37-46, of record). This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Instant claims 18, 19, 51 and 52 recite "said variable region being devoid of normal light chain interaction sites, whereas the claims 18, 23, 24, 26 and 27 of '900 recite "heavy chain immunoglobulin(s)...naturally devoid of light chains."

Evidentiary reference van der Linden *et al* teach that that the IgG *Camelid* heavy chain antibody is [naturally] devoid of the immunoglobulin light chain. van der Linden *et al* further teach that the variable fragments of heavy chain antibodies (VHH) do not have the hydrophobic interface which is important in the formation of a functional "classical" antibody molecule, composed of heavy and light chains, *i.e.,* lack interaction sites for light chain binding (page 38 at the first full paragraph at column 1).

The humanized immunoglobulin recited in claims 24 and 25 of copending '900 are obvious variants of the immunoglobulins of the instant claims. Claim 54 is included in this rejection because an immunoglobulin that specifically binds a protein on tumor cells is an obvious variant of an immunoglobulin. Claim 53 is included in this rejection because an immunoglobulin that specifically binds a protein, hapten, carbohydrate or nucleic acid antigen is an obvious variant of an immunoglobulin.

10. Claims 33 and 35 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 18-27 of copending Application No. 11/350,900 in view of Harlow and Lane (of record). This is a provisional obviousness-type double patenting rejection.

Claims 33 and 35 are drawn to a VHH immunoglobulin or fragment thereof labeled with a detectable label (claim 33) that is a radioisotope, an enzymatic marker, or chemiluminescent marker (claim 35).

Claims 18-27 of '900 are drawn to a VHH immunoglobulin that is not labeled with a detectable label.

Harlow and Lane teach labeling antibodies with radioisotopes, enzymatic markers or flurochromes (*i.e.,* chemiluminescent markers) for the purpose of immunoassay (page 591).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have labeled the immunoglobulins recited in claims 18-27 of '900 with the detectable labels taught by Harlow and Lane.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this to prepare immunoglobulins recited in the claims of '900 that are suitable for immunoassay as taught by Harlow and Lane.

Applicant has not addressed this rejection.

11. Claims 18-22, 25-27, 31, 32 and 51-54 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 6,005,079 (of record) as evidenced by WO 94/25591 (of record), by an admission in the instant specification on page 13 at paragraphs 2-5, and as evidenced by van der Linden *et al* (Biochimica et Biophysica Acta 1999, 1431: 37-46, of record). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of '079 are encompassed by the instant claims.

The claims 1-14 of U.S. Patent No. 6,005,079 are drawn to an immunoglobulin (or fragment thereof) comprising two heavy polypeptide chains, each heavy chain containing a binding site specific for an antigen, said immunoglobulin containing a variable (VHH) region and a constant region, said constant region being devoid of the CH1 domain and wherein the immunoglobulin is devoid of light chains, including wherein the immunoglobulin is obtainable by adsorption by affinity chromatography on Protein A, but not protein G (*i.e.,* is IgG2), or is absorbed by both Protein A and by Protein G (*i.e.,* is IgG3), and including wherein the molecular weight is about 100Kd non-reduced and about 45 kD reduced, and wherein position 45 is not leucine, but rather is cysteine or a charged amino acid residue.

Evidentiary reference WO 94/25591 teaches the presence of considerable amounts of IgG like material of 100 Kd in the serum of the camel and that these molecules are composed of heavy chain dimers and are devoid of light chains. WO 94/25591 further teaches that these molecules bear an extensive antigen binding repertoire, and that camel heavy chain IgGs lack the CH1, which in one IgG class might be structurally replaced by an extended hinge. WO 94/25591 teaches that heavy chain IgGs are a feature of all *Camelids*. WO 94/25591 teaches that by a combination of affinity chromatography on Protein A and Protein G, three quantitatively important fractions corresponding to subclasses of IgG can be isolated from the serum of camels, two of which contain molecules of about 100 Kd, which upon reduction yield only heavy chains of 46 Kd (IgG2 fraction binding only to Protein A) and 43 Kd (IgG3 fraction binding to

Protein A and Protein G), and both classes lack the light chain completely (see entire reference, especially page 1 at lines 18-32, page 2 at lines 1-4).

The admission in the instant specification on page 13 at paragraphs 2-5 is that a difference between normal 4 chain immunoglobulins and camelid VHH immunoglobulins is the presence of leucine (98%), proline (1%) or glutamine (1%) at position 45 *versus* arginine, glutamic acid (*i.e.,* charged amino acid residues) or cysteine at position 45.

Evidentiary reference van der Linden *et al* teach that that the IgG *Camelid* heavy chain antibody is [naturally] devoid of the immunoglobulin light chain. van der Linden *et al* further teach that the variable fragments of heavy chain antibodies (VHH) do not have the hydrophobic interface which is important in the formation of a functional "classical" antibody molecule, composed of heavy and light chains, *i.e.,* lack interaction sites for light chain binding (page 38 at the first full paragraph at column 1).

Claim 54 is included in this rejection because an immunoglobulin that specifically binds a protein on tumor cells is an obvious variant of an immunoglobulin. Claim 53 is included in this rejection because an immunoglobulin that specifically binds a protein, hapten, carbohydrate or nucleic acid antigen is an obvious variant of an immunoglobulin.

Applicant has not addressed this rejection.

12. Claims 33 and 35 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 6,005,079 (of record) in view of Harlow and Lane (of record).

Claims 33 and 35 are drawn to a VHH immunoglobulin or fragment thereof labeled with a detectable label (claim 33) that is a radioisotope, an enzymatic marker, or chemiluminescent marker (claim 35).

Claims 1-14 of '079 are drawn to a VHH immunoglobulin or fragment thereof that is not labeled with a detectable label.

Harlow and Lane teach labeling antibodies with radioisotopes, enzymatic markers or flurochromes (*i.e.,* chemiluminescent markers) for the purpose of immunoassay (page 591).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have labeled the immunoglobulins recited in claims 18-27 of '079 with the detectable labels taught by Harlow and Lane.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this to prepare immunoglobulins recited in the claims of '079 that are suitable for immunoassay as taught by Harlow and Lane.

Applicant has not addressed this rejection.

13. Claims 18-22, 25-27, 31-33, 35 and 51-54 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 5,840,526 (of record) as evidenced by an admission in the instant specification on page 13 at paragraphs 2-5 and by van der Linden *et al* (Biochimica et Biophysica Acta 1999, 1431: 37-46, of record) and WO 94/25591 (of record). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of '526 are encompassed by the instant claims.

The claims 1-10 are drawn to an immunoglobulin comprising two heavy polypeptide chains, each heavy chain consisting of a complete antigen binding site, said immunoglobulin containing a VHH region and a constant region, said constant region being devoid of polypeptide light chains, and wherein the variable region contains at position 45 an amino acid which is not a leucine, proline or glutamine residue, and including wherein the amino acid sequence is partially defined.

The admission in the instant specification on page 13 at paragraphs 2-5 is that a difference between normal 4 chain immunoglobulins and camelid VHH immunoglobulins is the presence of leucine (98%), proline (1%) or glutamine (1%) at position 45 *versus* arginine, glutamic acid (*i.e.,* charged amino acid residues) or cysteine at position 45. Evidentiary reference van der Linden *et al* teach that that the IgG *Camelid* heavy chain antibody is [naturally] devoid of the immunoglobulin light chain. van der Linden *et al* further teach that the variable fragments of heavy chain antibodies (VHH) do not have the hydrophobic interface which is important in the formation of a functional "classical" antibody molecule, composed of heavy and light chains, *i.e.,* lack interaction sites for light chain binding (page 38 at the first full paragraph at column 1).

Evidentiary reference WO 94/25591 teaches the presence of considerable amounts of IgG like material of 100 Kd in the serum of the camel and that these molecules are composed of heavy chain dimers and are devoid of light chains. WO 94/25591 further teaches that these molecules bear an extensive antigen binding repertoire, and that camel heavy chain IgGs lack the CH1, which in one IgG class might be structurally replaced by an extended hinge. WO 94/25591 teaches that heavy chain IgGs are a feature of all *Camelids*. WO 94/25591 teaches that by a combination of affinity chromatography on Protein A and Protein G, three quantitatively important fractions corresponding to subclasses of IgG can be isolated from the serum of camels, two of which contain molecules of about 100 Kd, which upon reduction yield only heavy chains of 46 Kd (IgG2 fraction binding only to Protein A) and 43 Kd (IgG3 fraction binding to

Protein A and Protein G), and both classes lack the light chain completely (see entire reference, especially page 1 at lines 18-32, page 2 at lines 1-4).

Claim 54 is included in this rejection because an immunoglobulin that specifically binds a protein on tumor cells is an obvious variant of an immunoglobulin.

Applicant has not addressed this rejection.

14. Claims 18-22, 25-27, 31-33, 35 and 51-54 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-24 of U.S. Patent No. 6,765,087 (of record) as evidenced by van der Linden *et al* (Biochimica et Biophysica Acta 1999, 1431: 37-46, of record). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of '087 are encompassed by the instant claims.

Evidentiary reference van der Linden *et al* teach that that the IgG *Camelid* heavy chain antibody is [naturally] devoid of the immunoglobulin light chain. van der Linden *et al* further teach that the variable fragments of heavy chain antibodies (VHH) do not have the hydrophobic interface which is important in the formation of a functional "classical" antibody molecule, composed of heavy and light chains, *i.e.,* lack interaction sites for light chain binding (page 38 at the first full paragraph at column 1).

Claim 54 is included in this rejection because an immunoglobulin that specifically binds a protein on tumor cells is an obvious variant of an immunoglobulin.

Applicant has not addressed this rejection.

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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